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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/330,903	06/11/1999	IGOR GONDA	6513/061US1	9995

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	27

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/330,903	GONDA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-64 and 66-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-64 and 66-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/22/03 has been entered.

Applicant's amendments to the claims submitted 9/23/02 have been entered. Note that these amendments were not entered when submitted due to an inadvertant error by the Examiner, in which the wrong box was checked in item 5 of the PTO form 303. Note further that the amendment was responded to completely by the Examiner in the Advisory Action, as if it had been entered.

Claim 65 was canceled as requested. Claims 21-56 were previously canceled by amendment.

Claims 57-64, and 66-71 are pending and under consideration in this Office Action.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 112 as follows:

The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first

application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

This Application claims priority to application number 08/752,946, filed 11/21/96, now US Patent 5,906,202, issued 5/25/99. However, instant claims 57-64, and 66-71 recite "a polynucleotide and a condensing agent" and there is no support for this limitation in US Patent 5,906,202. Furthermore, '202 provides no support for the following claim limitations, a lipid-based carrier (instant claims 61 and 62). For these reasons, the priority date for the instant claims is considered to be that of provisional application 60/089,146 which is 6/12/98.

Rejections Withdrawn

The rejection of claim 66 under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's amendment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-64, and 66-71 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 57-64, and 66-71 are indefinite because they require a result without any process that could lead to the results. More particularly, step (c) of claim 57 recites the phrase "wherein aerosol particles are comprised of a polynucleotide and a condensing agent which results in condensing polynucleotide particles". The claims are indefinite because a composition cannot have a result. Only processes can have results, and the claim recites no steps which can lead to condensing polynucleotide particles. As written, it is unclear as to whether the nucleic acid particles of the composition must be condensed to a size in the range of from about 20-50 nm, or whether the composition need only comprise a condensing agent capable of condensing the nucleic acid to this size. **For the purpose of examination under 35 USC 103, these claims have been interpreted broadly to require only the presence of a condensing agent capable of condensing nucleic acids to the recited size range.**

Applicant has not responded to this ground of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 57-60, 70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al (US Patent 5,906,202, issued 5/25/99) in view of Debs

(US Patent 5,756,353, issued 5/26/98), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91).

Schuster teaches a device and method of delivering a volume of aerosol to a target area of a lung. The method comprises measuring a volume of particle-free air inhaled into the lungs, drawing a measured volume of aerosol into the respiratory tract, and inhaling an additional volume of particle-free air, insufficient to fill the upper region of the patient's respiratory tract. Each of these three inhalation volumes is controlled. See e.g. claim 3 at column 38. Schuster teaches the delivery of gene vectors by this method. See column 2, line 33; paragraph bridging columns 30 and 31, and claims 11-13. The method involves adjusting the size of aerosol particles during delivery. Schuster teaches using aerosol particle sizes from 1-10 microns in aerodynamic diameter, and the adjustment of particle size in order to target specific regions of lung. See item c or claim 1; column 12, lines 37, 38, and 47-49; column 20, lines 30-50; and paragraph bridging columns 20 and 21. Schuster also teaches adjusting inspiratory flow rate to 0.2 to 3 liters per second. See claim 14; and column 12, lines 34-36. Note that the instant specification at page 27, lines 17-19 states that the device of Schuster is useful for the instant method. Note also that the specification states in that same passage that the Schuster patent was commonly owned at the time of filing (see double patenting rejections below). Under 35 USC 103 (a) and (c), the Schuster patent is considered prior art because the instant Application was filed prior to 11/29/1999.

Schuster does not teach the use of a condensing agent, nor does Schuster explicitly distinguish between delivery to alveoli, central airways and upper airways.

Debs teaches a method of targeting an area of a patient's respiratory tract by delivering to the patient an aerosol comprising DNA condensed with cationic lipids. See abstract and column 11, lines 24-26. The lipid may be DOTAP or DOTMA. See claim 3, column 15. The size of the aerosol particles is adjusted based on the intended delivery site within the respiratory tract. A size range of from 0.5-5 microns is suggested for alveoli, and a size range of 4-12 microns is suggested for airway delivery. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16.

Radhakrishnan teaches that depth of penetration of aerosol particles into the respiratory tract is inversely related to the aerodynamic diameter of the particles, and discloses what size particles will reach various parts of the lung. See e.g. Fig. 3.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the delivery device and method of Schuster in the method of Debs. One would have been motivated to do so because Debs teaches that the choice of a nebulizer system will vary with the choice of target site (see column 12, lines 37-47) and Schuster teaches a single device and method which allow efficient targeting of the aerosol particles to desired areas of the lung. See column 2, lines 4-9. Debs teaches the entire range of aerosol particle sizes recited in the instant claims, and it was well-recognized in the prior art, in view of each of the cited references, that different areas of the respiratory tract could be targeted by different sized aerosol particles. It would have been obvious to adjust the size of aerosol particles to particular aerodynamic diameters in order to target various sites in the respiratory tract, because both Debs and Schuster suggest that this should be done. The size of the particles is clearly a result

effective variable, the optimization of which is routine in the art particularly in view of Radhakrishnan who establishes the relationship between particle size and depth of penetration into the respiratory tract.

Thus the invention as a whole was *prima facie* obvious.

Claims 57-64, and 66-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al (US Patent 5,906,202, issued 5/25/99) in view of Gao et al (US Patent 5,795,587, issued 8/18/98), Debs (US Patent 5,756,353, issued 5/26/98), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91).

The teachings of Schuster, Debs, and Radhakrishnan are summarized above, and can be combined to render obvious a method of targeting an area of a patient's respiratory tract by delivering an aerosol containing a condensed polynucleotide while adjusting both the particle size in the aerosol and the volume inhaled.

While these references teach aerosol particles comprising polynucleotides condensed with a cationic lipid, they do not teach aerosol particles comprising a polynucleotide, a condensing agent, and "further comprising a cationic lipid".

Gao teaches stable lipid-comprising nucleic acid delivery particles in which the nucleic acid is complexed with polycations. See column 9, line 40 to column 10 line 11, especially column 10, lines 6-11. See also claims 4 and 11. The particles may be delivered as an aerosol. See column 11, lines 30-34. The cationic lipid may be DOTAP, DOTMA, or DC-chol. See column 7, lines 30-64. The polycation may be a polyamine such as polylysine, protamine, spermine, or spermidine. See column 9, lines 40-53.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the device Schuster to create and deliver the compositions of Gao. One would have been motivated to do so because Gao suggests aerosol delivery, because Debs teaches that the choice of a nebulizer system will vary with the choice of target site (see column 12, lines 37-47), and because Schuster teaches a single device and method which allow efficient targeting of the aerosol particles to desired areas of the lung. See column 2, lines 4-9. Debs teaches the entire range of aerosol particle sizes recited in the instant claims, and it was well-recognized in the prior art, in view of the cited references, that different areas of the respiratory tract could be targeted by different sized aerosol particles. It would have been obvious to adjust the size of aerosol particles to particular aerodynamic diameters in order to target various sites in the respiratory tract, because both Debs and Schuster suggest that this should be done. The size of the particles is clearly a result effective variable, the optimization of which is routine in the art particularly in view of Radhakrishnan who establishes the relationship between particle size and depth of penetration into the respiratory tract.

Thus the invention as a whole was prima facie obvious.

Claims 57 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al (US Patent 5,906,202, issued 5/25/99) in view of Gao et al (US Patent 5,795,587, issued 8/18/98), Debs (US Patent 5,756,353, issued 5/26/98), Radhakrishnan (US Patent 5,049,389, issued 9/17/91), and Chu et al (US Patent 6,030,834, issued 2/29/00).

The teachings of Schuster, Gao, Debs, and Radhakrishnan are discussed above. These references do not teach the use of putrescine as a polycationic nucleic acid condensing agent.

Chu teaches that polycationic condensing agents include polylysine, polyarginine, polyornithine, protamine, spermine, spermidine, and putrescine. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the prior art clearly considered putrescine to be equivalent to protamine, spermine, and spermidine as a nucleic acid condensing agent.

Thus the invention as a whole was prima facie obvious.

Claims 57 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al (US Patent 5,906,202, issued 5/25/99) in view of Gao et al (US Patent 5,795,587, issued 8/18/98), Debs (US Patent 5,756,353, issued 5/26/98), Radhakrishnan (US Patent 5,049,389, issued 9/17/91), and Curiel et al (US Patent 5,547,932, issued 8/20/96).

The teachings of Schuster, Gao, Debs, and Radhakrishnan are discussed above. These references do not teach the use of polyethyleneimine as a polycationic nucleic acid condensing agent.

Curiel teaches the use of polylysine, polyethyleneimine, protamine, spermine, and spermidine as DNA condensing agents, as well as the subsequent delivery of the condensed DNA to lung tissue by aerosol administration. See column 25, lines 21-32, and column 36, lines 6-17. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the prior art clearly considered polyethyleneimine to be equivalent to polylysine, protamine, spermine, and spermidine as a nucleic acid condensing agent.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicants arguments filed have been considered as they apply to the grounds of rejection set forth above, but are not persuasive. Applicant sets forth three basic

concepts in the instant invention and argues at page 6 of the response that the cited art does not teach any of the basic concepts alone or in combination. The three concepts are:

(1) a particle comprising a polynucleotide and a condensing agent;

(2) adjustment of aerosol particle size to target specific regions of lung; and

(3) controlling the volume of aerosol inhaled

Applicant's argument is unpersuasive. Debs teaches concept (1). See claim 3 at column 15. Each of Debs, Schuster, and Radhakrishnan teach concept (2). See Debs at column 12, lines 51-61, and claim 1, 14, 15, and 16. See Schuster at column 20, lines 30-50. See Radhakrishnan, Fig. 3. Schuster teaches concept 3 at, for example, claim 6 which bridges columns 38 and 39.

In the first full paragraph of page 6, Applicant argues that the cited art does not teach adjusting the size of the aerosol particles while also adjusting the inhaled volume of aerosol. This is incorrect. As noted above, Schuster teaches this concept at claim 6 which requires control over inhalation volume, and passage of particles through a membrane that adjusts the size of the particles. Applicant also argues that the cited art does not teach these concepts in combination with the use of a condensing agent. It is true that no single reference teaches this combination. However, the rejection is a made under 35 USC 103, not 102, so the combination of references is allowed.

Applicant argues in the second full paragraph of page 6 that the combination of Debs and Schuster is unrealistic because Debs does not teach toward adjustment of inhaled volume in order to target areas of the lung. This is unpersuasive because Debs

is not relied upon to teach adjustment of inhaled volume, Schuster teaches this. Applicant has not addressed the Office's stated of motivation to combine the references. One would have been motivated to use the device and method of Schuster to deliver the particles of Debs because while both Debs and Schuster recognize that the control of particle size allows one to target specific regions of the lung, Debs teaches that this can be accomplished by using nebulizers of different characteristics, whereas Schuster teaches a single device that allows selection of particle size simply by changing the membranes. Clearly one of ordinary skill in the art, aware of both teachings, would have been motivated to combine them. The remainder of Applicant's arguments are directed to the failure of the remaining references to make up for the supposed deficiencies in Debs and Schuster. These arguments are unpersuasive because, as shown above, Debs and Schuster are not deficient references.

For these reasons the rejections are maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57-60, 70, and 71 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,906,202 to Schuster in view of Debs (US Patent 5,756,353, issued 5/26/98), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91).

Claims 57-64, and 66-71 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,906,202 to Schuster in view of Gao et al (US Patent 5,795,587, issued 8/18/98), Debs (US Patent 5,756,353, issued 5/26/98), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91).

Claims 57 and 68 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,906,202 to Schuster in view of Gao et al (US Patent 5,795,587, issued 8/18/98), Debs (US Patent 5,756,353, issued 5/26/98), Radhakrishnan (US Patent 5,049,389, issued 9/17/91), and Chu et al (US Patent 6,030,834, issued 2/29/00).

Claims 57 and 69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,906,202 to Schuster in view of Gao et al (US Patent 5,795,587, issued

8/18/98), Debs (US Patent 5,756,353, issued 5/26/98), Radhakrishnan (US Patent 5,049,389, issued 9/17/91), and Curiel et al (US Patent 5,547,932, issued 8/20/96).

The combinations of these references is discussed above under 35 USC 103 rejections.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.